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EXAMINER

GOLLAMUDI, SHARMILA S

ART UNIT	PAPER NUMBER
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1616

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/491,624

Applicant(s)

DARDER, CARLOS PICORNELL

Examiner

Sharmila S. Gollamudi

Art Unit

1616

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 August 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 15, 16, 18-25, 30, 31, 33, 34, 36 and 39-50 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15, 16, 18-25, 30, 31, 33, 34, 36 and 39-50 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1616

DETAILED ACTION

Receipt of Amendments/Remarks filed 8/30/06, Information Disclosure Statement filed 6/9/06, Rule 132 Declaration filed 7/10/06 is acknowledged. Claims 15-16, 18-25, 30-31, 33-34, 36, 39-50 are pending in this application. Claims 1-14, 17, 26-29, 32, 35, and 37-38 stand cancelled.

Claim Objections

The objection of claims 1, 3, 27, 31, 34, 36 are withdrawn in view of the amendments of 8/30/06

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-16, 18-25, 30-31, 33-34, 36, 39-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicant's arguments which are found to be persuasive.

Applicant has amended the independent claims to recite the aqueous or hydroalcoholic solution comprises an active ingredient of the general formula I or general formula II or III, an alkaline reacting compound, at least one pharmaceutically acceptable excipient. It is unclear if the alkaline reacting compound is part of the Markush group recited for the active ingredient. For instance, is the Markush group an active ingredient of the general formula I, general formula II, general formula III, or an alkaline reacting compound? The examiner notes the independent claims have a “-“ next to each required element (for instance “- an active ingredient” and “- at least one pharmaceutically acceptable excipient”); however the recited “alkaline reacting

Art Unit: 1616

compound” is not noted with a “-“, which implies it is part of the active ingredient Markush group. It appears applicant is intending to claim the alkaline reacting compound as a required element separate from the active ingredient Markush group. However, further clarification or claim reconstruction is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The rejection of claims 1-13, 26-29, 35, and 37-38 under 35 U.S.C. 102(e) as being anticipated by US Patent 6,132,771 to Depui et al is moot in view of the cancellation of claim 1.

The rejection of claims 1-13 and 15-40 under 35 U.S.C. 102(e) as being anticipated by US Patent 6,365,184 to Depui et al is withdrawn for the following reasons: It is unclear if US '184 utilizes the same apparatus, i.e. a Wurster-equipped fluidized apparatus, in all three steps.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of claims 1-13, 26-29, 35, and 37-38 under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,132,771 to Depui et al. is moot in view of the cancellation of claim 1.

Claims 15-16, 18-25, 30-31, 33-34, 36, 39-46, 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,365,184 to Depui et al by itself or in view of Wurster (2,799,241).

Depui et al teach an oral pharmaceutical dosage form comprising a proton pump inhibitor and an NSAID (abstract). More specifically, Depui et al teach that the proton pump inhibitor can be selected from omeprazole, lansoprazole, pantoprazole, pariprazole, and leminoprazole. See column 4 to 6. Additionally, Depui teaches that the core material for their composition is a seed layered with the proton pump inhibitor along with an enteric coating. See column 8, lines 48-50. Depui et al. also disclose that the seeds can be made of different materials, including sugars and mixtures thereof. See column 8, line 58. The reference discloses mixing the proton pump inhibitor with other components prior to layering on the seeds, wherein the components can include binders, surfactants, disintegrating agents, and fillers. See column 9, lines 1-5. The binder can be selected from HPM, HPMC, CMC, PVP, sugars and starches. See column 9, lines

Art Unit: 1616

3-6. The alkaline substance can be selected from sodium, potassium, calcium, magnesium and aluminum salts or phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminum hydroxide/sodium bicarbonate co precipitate; substances normally used in antacid preparations such as aluminum, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as Al.sub.2 O.sub.3 , 0.6MgO.CO.sub.2 O , 0.12H.sub.2 O , $(\text{Mg.sub.6 Al.sub.2 (OH).sub.16 CO.sub.3 0.4H.sub.2})$, $\text{MgO.Al.sub.2 O.sub.3}$, $0.2\text{SiO.sub.2.nH.sub.2 O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances. See column 9, lines 27-42. The surfactant disclosed is sodium lauryl sulfate. See column 9, lines 10. Lactose monohydrate and mannitol are utilized in the examples. Depui et al disclose that the seeds have a size between 0.1 and 2 mm, which equals 100 to 2000 micrometers. See column 8, line 62. Most importantly, Depui et al state that their formulation does not necessarily include a spacing layer between the coated seed and an enteric coating. Depui et al disclose the middle, separating layer is **optional**, and the enteric coating can be applied directly to the coated core. Depui et al. disclose the optionally applied separating layer(s) is not essential for the invention. See column 9, lines 46-50 and column 10, lines 41-43. The enteric coating layer is selected from I-IPMCP, methacrylic acid polymers, HPMC acetate succinate, and shellac. See column 10, lines 46-53. Further, the enteric coating layer includes a plasticizer: PEG or cetyl alcohol, anti-tacking agents, and pigments. See column 10, lines 58-60 and column 11, lines 1-10. Depui teaches using suitable equipment such as a coating pan, coating granulator, or a fluidized bed apparatus to apply the coats.

Art Unit: 1616

Example 4 utilizes a fluid bed apparatus to coat the inert seeds with the active. Then a **Wurster-equipped fluidized apparatus** is used to sub-coat the separating layer, followed by coating an enteric coating using the same equipment. See example 4. Further, arginine is utilized in example 4.

Although example 4 teaches the use of a fluidized bed apparatus in all three steps and Depui teaches the specific use of a Wurster-equipped fluidized apparatus in the second and third step, it is unclear if the same apparatus, i.e. a Wurster-equipped fluidized apparatus, is used in the first step. Depui teaches using a fluidized bed apparatus in the first step without specifying the type.

Wurster teaches the Wurster-type fluidized apparatus provides for a uniformed coating and preventing the coating material from sticking to the inner surface of the chamber. See column 1, lines 22-35.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to look to the guidance provided by Depui and utilize a Wurster-equipped fluidized apparatus in all three steps since Depui teaches layering may be done by three different types of processes: 1) a coating pan; 2) coating granulator; 3) or a fluidized bed apparatus. Thus, although Depui does not specify that the fluidized bed apparatus in the first step is Wurster-equipped, it is the examiner's position that since all three steps are utilizing a similar process of spray coating using a similar apparatus, i.e. a fluidized bed apparatus, the process is prima facie obvious. Further, it would have been obvious to also use the Wurster-type fluidized bed apparatus in the first step with a *reasonable* expectation of similar results and success since Depui teaches the use of a fluidized bed apparatus without specificity in the first step and the

Art Unit: 1616

Wurster-type used in the second and third step is also a fluidized bed apparatus that functions to coat the pellet. Thus, regardless of the fluidized apparatus being a Wurster-type, the same end result is yielded, wherein the core is coated.

Alternatively, it would have been obvious to look at Wurster and utilize the instant apparatus in the first step. One would have been motivated to do so since Wurster teaches that the Wurster-type provides a uniform coating. Thus, a skilled artisan would have been motivated to use the same apparatus in the first step to provide a uniform coating so that all three coatings would uniformly be applied. Further, the Wurster patent demonstrates that the Wurster-Type apparatus is not a new type of apparatus and as been known in the art since the 1940s. Therefore, it is reasonable for a skilled artisan to utilize a conventional machine routinely utilized in the pharmaceutical coating art.

Response to Arguments

Applicant's arguments filed 8/30/06 have been fully considered but they are not persuasive.

Applicant argues that it is clear from the wording of example 4 that there are at least two operational apparatus employed.

The examiner has considered this argument and since the wording of example 4 is ambiguous if indeed one or two different equipment are used, the examiner has made a rejection under obviousness.

Applicant argues that the instant claim language excludes Depui's separating layer and thus the instant claims cannot be anticipated. Applicant argues that all examples have a separating layer between the active layer and enteric coating. It is argued that Depui fails to

Art Unit: 1616

enable such a dosage form. Applicant claims that Depui et al never exemplify an embodiment without a separating layer or alkaline substance. Applicant argues that Depui et al do not describe a stable and useful oral form of a proton pump inhibitor without an alkaline substance and at least one separating layer.

Firstly, the examiner further points out the process claims of 34 and 36 recite comprising language and thus it is not exclusionary, i.e. it does not exclude Depui's separating layer or other active ingredients. The instant claim language that the enteric coating layer is coated directly on the charged nucleus does not overcome the rejection for the following reasons: The examiner points out that the claims are given their broadest reasonable interpretation. As discussed above the instant claim language, comprising, which is not exclusionary. Thus, the "said charged nucleus" may include other layers. For instance, the inert nucleus, the drug, and the separating layer coated thereon may be interpreted to make-up "the charged nucleus". Thus, the amendment to independent claim 34 wherein the claim recites "gastro-resistant external coating layer on said charged nucleus" and the amendment to independent claim 36 wherein the claim recites "an gastro-resistant external coating layer thereon", does not overcome the rejection.

Applicant argues that the examiner is "engaging in claim construction" and the examiner is only permitted to interpret the as broadly as reasonably supported by the specification and the specification does not utilize a second active e agent.

Applicant's arguments are not readily apparent. The examiner notes MPEP 2111.03 which clear defines how the "comprising" should be interpreted.

"The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) ("like the term

Art Unit: 1616

'comprising,' the terms 'containing' and 'mixture' are open-ended." < *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.);

Nowhere does MPEP state that applicant's specification should be relied upon to interpret the claim language "comprising".

Assuming arguendo that the claim language excluded a separating layer, the examiner point out the separating layer is **optional**. The Webster Dictionary defines *optional* as: involving an option: not compulsory. Further, option is defined as: 1) something that may be chosen 2) an item that is offered in addition to or in place of the standard. Thus, as noted by the applicant himself, the separating layer and alkaline substance are optional embodiments. The word "optional" in itself clearly denotes that if one were to exclude the *optional* separating layer and *optional* alkaline substance, it would not be detrimental to the dosage form. With regards to applicant's argument that if the separating layer is excluded, then Depui et al would not be stable and thus Depui is not enabled. Again, it is pointed out that if the separating layer was absolutely critical to Depui's invention, then Depui would not insert the word optional.

Applicant argues that the dictionary definition is not favored.

The examiner notes MPEP 2111.01, which clearly states that the claims must be given plain meaning unless clearly defined by the specification. Further, "plain meaning" refers to the ordinary and customary meaning given to the term by those skilled in the art. The examiner points out that word "optional" is not a term that has a special meaning to those in the art. The examiner merely uses the dictionary to clearly define to applicant that optional implies that it is

Art Unit: 1616

not necessary. This is further substantiated by Depui disclosure on column 9, lines 46-50 and column 10, lines 41-43, “the optionally applied separating layer(s) is not essential for the invention.”

Applicant argues that Depui et al. does not make a positive statement that a separating layer is not necessary. The examiner points to column 9, lines 46-50 and column 10, lines 41-43 wherein Depui et al disclose a middle, separating layer is **optional**, and the enteric coating can be applied directly to the coated core. Further, Depui et al. disclose “the optionally applied separating layer(s) is not essential for the invention.” See column 9, lines 46-50 and column 10, lines 41-43. This is clearly a “positive statement” that the separating layer is not necessary.

Applicant argues that Depui does not exemplify a dosage form without the optional separating layer.

The examiner points out that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiment. See *In re Susi*. Further, the examiner points out that Depui discloses two options with the use of the word “optional”, a dosage form with or without. Thus, a skilled artisan can immediately envisage the other form, i.e. the dosage form without a separating layer. Therefore, the courts have held that if one can immediately envisage an embodiment, then it is held to be anticipated. See *In re Petering* 133 USPQ 275 (CCPA 1962).

Applicant argues that the examiner has repeatedly ignored the Declarations by stating there are not persuasive. Applicant argues that a declaration can be used to demonstrate that the prior art is not enabling. Further, applicant argues that the examiner has also made the rejection under obviousness and thus the declaration must be addressed.

Art Unit: 1616

Applicant argues that the Molina affidavit demonstrates that Depui is not enabled. Applicant argues that this declaration has been repeatedly ignored. Applicant argues that the Johansson's declaration demonstrates that Depui is not enabling. Applicant argues that the instant example 1 is more stable than Depui's example 5.

It is unclear as to why the applicant repeatedly asserts the examiner has not considered the declaration. The record clearly indicates the examiner and previous examiner have considered the declaration and the examiner provides a detailed analysis as to why the declarations are not persuasive. Apparently, applicant does not agree with the examiner's reasoning and views a withdrawal of the rejection as the only means in which a declaration is "considered". Again the examiner points out that stating the "declaration is not persuasive" and providing reasons is not equivalent to applicant's assertion that it has not been considered.

The examiner notes that in the Molina declaration, applicant attempts to overcome Depui by showing EP '797 claims to make a stable granule and does not. The examiner points out that if applicant contends that the prior art is not enabling and in instant case, applicant contends Depui is not enabling, then the declaration must show that Depui is not enabled. Applicant's demonstration that EP '797 does not make a stable granule does not extend to Depui. Depui is a different invention with no relation to EP '797. Further, EP '797 teaches a different formulation than Depui. Applicant has not addressed this.

With regard to the Johansson's declaration, the examiner notes that the Declaration states that "The results obtained in working Example 5 of US 6.132.771 where not a surprise for me, because the prior art, for instance EP0247983 (US 4,786,505) and EP244380 (US 4,853,230) cited in the patent application taught that an inert separating layer should be place between the

Art Unit: 1616

core material and the outer enteric coating layer to avoid the contact between the anti-ulcer benzimidazole compound (omeprazole, lansoprazole, pantoprazole. etc.) and the acidic component (methacrylic copolymer) of the enteric layer. Is it also mentioned that benzimidazole compounds are not stable in acidic medium, and in contact with acidic compounds they suffer degradation and develop a strong color.”

Firstly, the examiner again points out that the instant rejection is made over US 6,365,184 and not US 6,132,771. Further, US ‘184 uses a fluid bed apparatus to make the composition. Thus, applicant must show that US ‘184 is not enabling. A showing that US ‘771 is not enabling does not extend to instant rejection.

Additionally, the examiner however notes the following: The examiner points out that the instant invention as claimed is directed to the same dosage as disclosed by Depui et al. For instance, applicant argues that the instant invention does not require Depui’s optional separating layer and still is stable. However, as discussed above, the broadest reasonable interpretation is given to the claims, and it is the examiner’s position that the claim does not exclude a separating layer. Assuming arguendo that the claims do exclude the separating layer, the examiner notes that the instantly claimed invention requires the core material that comprises the anti-ulcer benzimidazole compound (omeprazole, lansoprazole, pantoprazole. etc.), a alkaline reaction compound, and an enteric coating polymer wherein the instant example 1 that the applicant utilizes is an acidic polymer. The prior art discloses this except the prior art discloses an optional separating layer. It is unclear how the instant formulation is stable versus the prior art’s formulation if the only difference is the separating layer, which applicant’s argues provides stability to Depui’s dosage form. The same dosage form is being claimed; thus the same

Art Unit: 1616

interaction must take place. The examiner points out that the distinguishable feature must be claimed since applicant's arguments are on the basis that the prior art is not enabled for a stable formula and the instant invention is. If applicant removes the stabilizing separating layer what makes the instant invention stabilizing without it?

Applicant attributes the stability to the non-porous layer; however the instantly claimed layer is not distinguishable from Depui. Applicant argues that Depui's active layer is porous but does not specify what exactly makes it porous. As discussed previously, it is the examiner's position that Depui's active layer has the same components as the instant claims and the instant examples; thus it is non-porous. Applicant's arguments of 10/31/05, especially page 11-12 imply that the reaction alkaline compound can cause the layer to be porous, however the instant claims also have an alkaline reaction compound. Thus, applicant cannot claim the alkaline reaction compound in all the independent claims and yet argue against its use. The applicant's arguments are contradicting the applicant's claim itself.

Applicant attributes this stability to the process of making the composition;

Applicant has argued that the process of making the instant invention, i.e. utilizing a Wurster fluidized bed coater, lends to the stability (Response of 10/31/05, 12/3/04 and affidavit of 11/22/02). However Depui uses a fluid bed apparatus and specifically a Wurster-fluidized apparatus in example 4. Although it is unclear if the same apparatus is used in all three steps, it is the examiner's position that the process will yield a similar result since the same type of machine is used. It is noted on page 16 of the instant specification states that a Wurster-type fluid bed apparatus or a similar apparatus may be used. Applicant has not compared the instant process using a Wurster-type fluidized apparatus compared to another fluidized bed apparatus.

Art Unit: 1616

Moreover, applicant has not provided any evidence that using a Wurster-type fluidized bed apparatus in all three steps compared to using a unspecified fluidized bed apparatus in the first step, followed by using the instant Wurster-type fluidized apparatus provides any unexpected product. For instance, the Rule 132 declaration compares the stability of Depui's formulation with or without the separating layer to show that Depui is supposedly non-enabling but the declaration does not provide any unexpected results pertaining to the apparatus itself. Further, it is unclear from this declaration and results if applicant's stability is due to the Wurster bed coater. The examiner suggests providing evidence wherein two formulas with the same components are made by different apparatuses.

Lastly, the examiner points out that Johansson's declaration states that the prior art's tablets are discolored compared the instant invention and this discoloration shows a degradation of the active and is unacceptable. The standard for demonstrating that a reference is not enabling is high. The examiner points out that to demonstrate that a reference is not enabling, the applicant must demonstrate that a pellet cannot be made. Clearly, a pellet was made, regardless of the color. With regard to any showings of unexpectedness based on a 103 rejection, it is pointed out that the discoloration only appeared after an hour. Thus, the claims do not recite how long the instant pellets are stable for. Clearly, as evidenced by the declaration, the pellets are stable for at least one hour. Moreover, the examiner points out that applicant's declaration is solely based on color to show degradation of the active. However, discoloration does not necessarily mean the active has degraded. The discoloration may be due to the interaction of other components. Applicant has not provided any data showing a chemical analysis of the active

Art Unit: 1616

and its purported degradation. The mere assertion that the discoloration means that the active has degraded is not enough to show that the prior art is not stable.

Furthermore, the examiner notes that the claims are not commensurate in scope.

Applicant relies on example 1 of the instant specification to demonstrate that the prior art is not enabled. Example 1 of the instant specification teaches a charged nucleus and the enteric coating with specific materials whereas the instant claims are broadly directed at least one excipient. As discussed above, applicant claims the same dosage form and states the difference between the prior art and the instant invention is the use of a separating layer. Further, applicant argues this separating layer in the prior art function to provide stability. Thus, the question is, how does applicant obtain a stable pellet by removing the stabilizing stable layer? It is noted that inventive example 1 the charged nucleus and the enteric coat comprises the components of the prior art's separating layer. For instance, the Depui's separating layer (example 4) comprises HPMC, PEG 6000, and talc whereas although the instant invention excludes the separating layer, the charged nucleus composition comprises HPMC and the enteric coating composition comprises talc and PEG 6000. **Thus, if applicant's stability is due to adding the very components that make-up the prior art separating layer, to the charged nucleus and enteric coating respectively and thus eliminating the need for the prior art's separating layer, then applicant must claim this.** Further, specific excipients are utilized in specific concentrations and it is unclear if the excipient and its concentrations contribute to the stability. Lastly, the examiner notes that applicant's independent claims are drawn to several different classes of compounds and applicant emphasizes the stability of the compounds. Applicant's Rule 132 is directed t showing that a single species lanzoprazole in a specific formula is stable. However, a single species cannot

Art Unit: 1616

apply to a genus and applicant has not shown that one can formulate a stable composition with each of the claimed class of active compounds. Thus, the claims must be commensurate with the scope.

Claims 15-16, 18-25, 30-31, 33-34, 36, 39-46, 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,132,771 to Depui et al in view of Ohno et al (4,017,647) or Wurster (2,799,241) respectively.

Depui et al teach an oral pharmaceutical dosage form comprising a proton pump inhibitor (abstract). More specifically, Depui et al teach that the proton pump inhibitor can be selected from omeprazole, lansoprazole, pantoprazole, pariprazole, and leminoprazole. See column 4 to 6. Additionally, Depui teaches that the core material for their composition is a seed layered with the proton pump inhibitor along with an enteric coating. See column 8, lines 48-50. Depui et al. also teach that the seeds can be made of different materials, including sugars and mixtures thereof. See column 8, line 58. The reference discloses mixing the proton pump inhibitor with other components prior to layering on the seeds, wherein the components can include binders, surfactants, disintegrating agents, and fillers. See column 9, lines 1-5. The binder can be selected from HPM, HPMC, CMC, PVP, sugars and starches. See column 9, lines 3-6. The alkaline substance can be selected from sodium, potassium, calcium, magnesium and aluminum salts or phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminum hydroxide/sodium bicarbonate co precipitate; substances normally used in antacid preparations such as aluminum, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 0.6\text{MgO} \cdot \text{CO}_2 \cdot 0.12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 0.4\text{H}_2\text{O}) \cdot \text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 0.2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or

Art Unit: 1616

similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances. See column 9, lines 27-42. The surfactant disclosed is sodium lauryl sulfate. See column 9, lines 10. Lactose monohydrate and mannitol are utilized in the examples. The instant plasticizers are taught. Depui et al teach that the seeds have a size between 0.1 and 2 mm, which equals 100 to 2000 micrometers. See column 8, line 62. Most importantly, Depui et al state that their formulation does not necessarily include a spacing layer between the coated seed and an enteric coating. Depui et al disclose a middle, separating layer is **optional**, and the enteric coating can be applied directly to the coated core. See column 9, lines 46-50 and column 10, lines 41-43. The enteric coating layer is selected from I-IPMCP, methacrylic acid polymers, HPMC acetate succinate, and shellac. See column 10, lines 46-53. Further, the enteric coating layer includes a plasticizer: PEG or cetyl alcohol, anti-tacking agents, and pigments. See column 10, lines 58-60 and column 11, lines 1-10.

Depui et al do not specify the type of fluidized bed apparatus utilized.

Ohno et al teach a method for providing an enteric coating on solid dosage forms. The enteric coating solution contains those taught in Depui et al, i.e. film-forming polymers (HPMC), plasticizers, pigments, etc. on column 2. Ohno et al teach the use of a conventional coating machine such as pan coaters, drum-type coaters, or Wurster-type fluidizing coaters, and Glatt fluidizing coater since there is no principle difference between coating solid dosage forms and all conventional coaters work under the same principle of utilizing a coating solution. See column 3, lines 24-40.

Art Unit: 1616

Wurster teaches the Wurster-type fluidized apparatus provides for a uniformed coating and preventing the coating material from sticking to the inner surface of the chamber. See column 1, lines 22-35.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Depui et al and Ohno et al and utilize the fluidized apparatus of choice such as instant Wurster-type. One would have been motivated to do so since Ohno teaches that the Wurster-type apparatus among other fluid bed coaters are known and conventionally utilized in the art for coating purposes and all the coating machines work under the same principle. Therefore, it is prima facie obvious to utilize the instant Wurster-Type in Depui's process with a reasonable expectation of success since not only does Depui teach the use of a fluid bed apparatus but Ohno teaches the equivalency of all coating machines.

Further, it would have been obvious to look at Wurster and utilize the instant apparatus. One would have been motivated to do so since Wurster teaches that the Wurster-type provides a uniform coating. Further, the Wurster patent demonstrates that the Wurster-Type apparatus is not a new type of apparatus and as been known in the art since the 1940s. Therefore, it is reasonable for a skilled artisan to utilize a conventional machine routinely utilized in the pharmaceutical coating art.

Response to Arguments

Applicant's arguments filed 8/30/06 have been fully considered but they are not persuasive.

Applicant argues that the Wurster-type fluidized apparatus provides for a uniform coating, which eliminates the need for a separating layer and still provide a stable dosage form.

Art Unit: 1616

Applicant argues that Ohno does not teach all coating apparatuses are equivalent and the examiner is not free to modify the disclosures.

The examiner's discussion pertaining to US '184 is incorporated herein.

Firstly, the examiner points out that process claims of 34 and 36 recite comprising language and thus it is not exclusionary, i.e. it does not exclude Depui's separating layer or other active ingredients. The instant claim language that the enteric coating layer is coated directly on the charged nucleus does not overcome the rejection for the following reasons: The examiner points out that the claims are given their broadest reasonable interpretation. As discussed above the instant claim language, comprising, which is not exclusionary. Thus, the "said charged nucleus" may include other layers. For instance, the inert nucleus, the drug and the separating layer coated thereon may be interpreted to make-up "the charged nucleus". Thus, the amendment to independent claim 34 wherein the claim recites "gastro-resistant external coating layer on said charged nucleus" and the amendment to independent claim 36 wherein the claim recites "an gastro-resistant external coating layer thereon", does not overcome the rejection.

Assuming *arguendo* that the claim language excluded a separating layer, the examiner point out the separating layer is **optional**. The Webster Dictionary defines *optional* as: involving an option: not compulsory. Further, option is defined as: 1) something that may be chosen 2) an item that is offered in addition to or in place of the standard. Thus, as noted by the applicant himself, the separating layer and alkaline substance are optional embodiments. The word "optional" in itself clearly denotes that if one were to exclude the *optional* separating layer and *optional* alkaline substance, it would not be detrimental to the dosage form. With regards to applicant's argument that if the separating layer is excluded, then Depui et al would not be stable

Art Unit: 1616

and thus Depui is not enabled. Again, it is pointed out that if the separating layer was absolutely critical to Depui's invention, then Depui would not insert the word optional.

Applicant argues that "There is not a single mention in this paragraph of a fluidized bed in connection with applying the active ingredient coating or the enteric coating. What is specifically mentioned is rotor granulation or extrusion/spheronization. As already established in the Molina Declaration, the use of rotor granulation produces an inferior and unacceptable product."

The examiner points to example 4 wherein all three steps use a fluidized apparatus. Thus, Depui clearly teaches a similar apparatus and similar process. The examiner notes that in the Molina declaration, applicant attempts to overcome Depui by showing EP '797 claims to make a stable granule and does not. The examiner points out that if applicant contends that the prior art is not enabling and in instant case, applicant contends Depui is not enabling, then the declaration must show that Depui is not enabled. Applicant's demonstration that EP '797 does not make a stable granule does not extend to Depui. Further, EP '797 teaches a different formulation than Depui. Applicant has not addressed this. The examiner further points out that applicant must compare a process using a fluidized bed apparatus compared to the instant Wurster-type fluidized apparatus. Applicant has not compared the closest prior art. Depui is a different invention with no relation to EP '797.

With regard to the Johansson's declaration, the standard for demonstrating that a reference is not enabling is high. Johansson's declaration states that the prior art's tablets are discolored compared the instant invention and this discoloration shows a degradation of the active and is unacceptable. The examiner points out that Johansson does not demonstrate that

Art Unit: 1616

US '771 is not enabling since clearly a pellet is made. The examiner points out that to demonstrate that a reference is not enabling, the applicant must demonstrate that a pellet cannot be made. With regard to any showings of unexpectedness based on a 103 rejection, it is pointed out that the discoloration only appeared after an hour. Thus, the claims do not recite how long the instant pellets are stable for. Clearly, as evidenced by the declaration, the pellets are stable for at least one hour. Moreover, the examiner points out that applicant's declaration is solely based on color to show degradation of the active. However, discoloration does not necessarily mean the active has degraded. The discoloration may be due to the interaction of other components. Applicant has not provided any data showing a chemical analysis of the active and its purported degradation. The mere assertion that the discoloration means that the active has degraded is not enough to show that the prior art is not stable.

Applicant attributes this stability to the process of making the composition. However, applicant has not compared the instant process using a Wurster-type fluidized apparatus compared to another fluidized bed apparatus. For instance, the Rule 132 declaration compares the stability of Depui's formulation with or without the separating layer to show that Depui is supposedly non-enabling but the declaration does not provide any unexpected results pertaining to the apparatus itself. Further, it is unclear from this declaration and results, if applicant's stability is due to the Wurster bed coater. The examiner suggests providing evidence wherein two formulas with the same components are made by different apparatuses. It is noted on page 16 of the instant specification states that a Wurster-type fluid bed apparatus or a similar apparatus may be used.

Art Unit: 1616

Additionally, the examiner however notes the following: The examiner points out that the instant invention *as claimed* is directed to the same dosage as disclosed by Depui et al. For instance, applicant argues that the instant invention does not require Depui's optional separating layer and still is stable. However, as discussed above, the broadest reasonable interpretation is given to the claims, and it is the examiner's position that the claim does not exclude a separating layer. Assuming *arguendo* that the claims do exclude the separating layer, the examiner notes that the instantly claimed invention requires the core material that comprises the anti-ulcer benzimidazole compound (omeprazole, lansoprazole, pantoprazole, etc.), a alkaline reaction compound, and an enteric coating polymer wherein the instant example 1 that the applicant utilizes is an acidic polymer. The prior art discloses this except the prior art discloses an optional separating layer. It is unclear how the instant formulation is stable versus the prior art's formulation if the only difference is the separating layer, which applicant's argues provides stability to Depui's dosage form. The same dosage form is being claimed; thus the same interaction must take place. The examiner points out that the distinguishable feature must be claimed since applicant's arguments are on the basis that the prior art is not enabled for a stable formula and the instant invention is. If applicant removes the stabilizing separating layer what makes the instant invention stabilizing without it?

Applicant attributes the stability to the non-porous layer; however the instantly claimed layer is not distinguishable from Depui. Applicant argues that Depui's active layer is porous but does not specify what exactly makes it porous. As discussed previously, it is the examiner's position that Depui's active layer has the same components as the instant claims and the instant examples; thus it is non-porous. Applicant's arguments of 10/31/05, especially page 11-12 imply

Art Unit: 1616

that the reaction alkaline compound can cause the layer to be porous, however the instant claims also have an alkaline reaction compound. Thus, applicant cannot claim the alkaline reaction compound in all the independent claims and yet argue against its use. The applicant's arguments are contradicting the applicant's claim itself.

Furthermore, the examiner notes that the claims are not commensurate in scope.

Applicant relies on example 1 of the instant specification to demonstrate that the prior art is not enabled. Example 1 of the instant specification teaches a charged nucleus and the enteric coating with specific materials whereas the instant claims are broadly directed at least one excipient. As discussed above, applicant claims the same dosage form and states the difference between the prior art and the instant invention is the use of a separating layer. Further, applicant argues this separating layer in the prior art function to provide stability. Thus, the question is, how does applicant obtain a stable pellet by removing the stabilizing stable layer? It is noted that inventive example 1 the charged nucleus and the enteric coat comprises the components of the prior art's separating layer. For instance, the Depui's separating layer (example 4) comprises HPMC, PEG 6000, and talc whereas although the instant invention excludes the separating layer, the charged nucleus composition comprises HPMC and the enteric coating composition comprises talc and PEG 6000. **Thus, if applicant's stability is due to adding the very components that make-up the prior art separating layer, to the charged nucleus and enteric coating respectively and thus eliminating the need for the prior art's separating layer, then applicant must claim this.** Further, specific excipients are utilized in specific concentrations and it is unclear if the excipient and its concentrations contribute to the stability. Lastly, the examiner notes that applicant's independent claims are drawn to several different classes of compounds and applicant

Art Unit: 1616

emphasizes the stability of the compounds. Applicant's Rule 132 is directed to showing that a single species lansoprazole in a specific formula is stable. However, a single species cannot apply to a genus and applicant has not shown that one can formulate a stable composition with each of the claimed class of active compounds. Thus, the claims must be commensurate with the scope.

With regard to Ohno, the examiner has cited the exact portion which applicant has argued the examiner has modified. Clearly, as acknowledged by applicant, Ohno teaches all the different coaters act under the same principle. This is sufficient to establish a prima facie case of obviousness. Moreover, Depui teaches a fluidized bed apparatus in all three steps. The only teaching lacking is the type of fluidized apparatus. Wurster teaches that the Wurster-equipped fluidized apparatus provides a uniform coating. Thus, it is the examiner's position absent unexpected results, that the a skilled artisan would have been motivated to specifically use the Wurster-equipped fluidized apparatus to provide a uniform coating. Further, applicant has not provided any evidence that the Wurster-type bed coater provide the unexpected results. For instance, the Rule 132 declaration compares the stability of Depui's formulation with or without the separating layer to show that Depui is supposedly non-enabling but the declaration does not provide any unexpected results. Further, it is unclear from this declaration and results if applicant's stability is due to the Wurster bed coater. The examiner suggests providing evidence wherein two formulas with the same components are made by different apparatuses. Secondly, the examiner points to column 3, lines 24-40 wherein Ohno clearly teaches: Any conventional coating machines, for example, pan coaters, rotary drum-type coaters, such as, Accela-Cota manufactured by Manesty Machines, England, Wurster-type fluidizing coaters developed by

Art Unit: 1616

Wisconsin Alumini Research Foundation, U.S.A., and fluidizing coaters such as that manufactured by Glatt, West Germany, may be employed in the method of the invention. There is no difference in principle between the conditions with which the solid dosage forms are coated in accordance with the invention and those with which the abovementioned conventional coaters are operated using a coating solution with an organic solvent.” Thus, it can be seen that the examiner has modified the teachings of the prior art.

Applicant argues that the instant process provides for a *substantially* non-porous homogenous layer. Firstly, it is noted that “substantially” is a broad term and is not defined by the specification. Secondly, the examiner points out that the combination of Depui and Ohno or Wurster respectively would also produce a substantially non-porous homogenous layer for the following reasons: Firstly, the prior art does not have to expressly state that which is inherent or implicit. It is the examiner’s position that Depui teaches a *substantially* non-porous homogenous layer. The claims are directed to “a *substantially* non-porous active layer or layer which disintegrates rapidly in water, made from a single aqueous or hydroalcoholic solution suspension which *comprises* the an active ingredient of anti-ulcer activity of general formula 1....and at least one pharmaceutically acceptable excipient selected from the groups which includes a binder, an alkaline reaction compound, a surface active agent, a filling material, and a disintegrating swelling excipient”. Depui discloses the seeds (inert nucleus) are layered with the proton pump inhibitor. Depui discloses the “proton pump inhibitor may be mixed with further components . Such components can be binders, surfactants fillers, disintegrating agents, alkaline additives or other and/or pharmaceutically acceptable ingredients alone or in mixtures. The binders are for example polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose

Art Unit: 1616

(HPC), carboxymethylcellulose sodium, polyvinyl pyrrolidone (PVP), or sugars, starches or other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.” See column 8, line 53 to column 9, line 10. The examiner points further points out that example 5 discloses lanzoprazole, sugar sphere seeds, hydroxypropylmethyl cellulose, sodium laurylsulfate, and water. Instant example 2 on page 18 of the instant specification discloses lanzoprazole, sodium lauryl sulphate, hydroxypropylmethyl cellulose, crystallized disodium phosphate, lactose, hydroxypropyl cellulose, and water. The instant example and Depui’s example 5 are similar and thus the layer must necessarily be non-porous. Again, the examiner points out that Depui need not explicitly state all inherent properties of the invention. It is noted that applicant has not pointed out specifically why Depui’s active layer is non-porous, i.e. what exactly makes 771’s allegedly porous. In fact applicant merely argues the prior art does not teach substantially non-porous homogenous layer but does not address the examiner’s rationale as to why Depui does teach a substantially non-porous homogenous layer.

Claims 15-16, 18-25, 30-31, 33-34, 36, 39-46, 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/01624 in view of Ohno et al (4,017,647) or Wurster (2,799,241).

WO 96/01624 teaches instant proton pump inhibitor in an oral dosage form comprising an inert core layered with the active agent, an optional separating layer, and an enteric layer. See examples and page 17, lines 24-30. The core may be prepared by spray drying. See page 12, lines 24-25. The inert seed is made of sugar, nonpareils, etc alone or in mixtures and is 0.1-2mm.

Art Unit: 1616

The inert seed is spray coated, using a layering equipment, with the instant active agent which is combined with other components such as binders, surfactants, instant fillers, surfactants, etc. see page 11, lines 5-26. WO 96/01624 teaches the instant proton pump inhibitor may be used in the neutral form or mixed with an alkaline salt such as sodium, potassium, calcium, and Al_2O_3 , 6MgOCO_2 , MgOAl_2O_3 , and basic amino acids. See page 5, lines 1-5 and page 12, lines 10-20. The instant enteric coating polymers are taught on page 13, lines 14-25 and the instant plasticizers are taught on page 15, lines 1-2. WO teaches the use of a fluid bed apparatus. Note examples, especially 1, wherein steps a) to c) are spray coated using a fluid bed apparatus. Example 11 teaches the core material without a separating layer.

WO does not specify the type of fluidized bed apparatus utilized.

Ohno et al teach a method for providing an enteric coating on solid dosage forms. The enteric coating solution contains those taught in Depui et al, i.e. film-forming polymers (HPMC), plasticizers, pigments, etc. on column 2. Ohno et al teach the use of a conventional coating machine such as pan coaters, drum-type coaters, or Wurster-type fluidizing coaters, and Glatt fluidizing coater since there is no principle difference between coating solid dosage forms and all conventional coaters work under the same principle of utilizing a coating solution. See column 3, lines 24-40.

Wurster teaches the Wurster-type fluidized apparatus provides for a uniformed coating an preventing the coating material from sticking to the inner surface of the chamber. See column 1, lines 22-35.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of WO '624 and Ohno et al and utilize the fluidized apparatus

Art Unit: 1616

of choice such as instant Wurster-type. One would have been motivated to do so since Ohno teaches that the Wurster-type apparatus among other fluid bed coaters are known and conventionally utilized in the art for coating purposes and all the coating machines work under the same principle. Therefore, it is prima facie obvious to utilize the instant Wurster-Type in WO's process with a reasonable expectation of success since not only does WO teach the use of a fluid bed apparatus but Ohno teaches the equivalency of all coating machines.

Further, it would have been obvious to look at Wurster and utilize the instant apparatus. One would have been motivated to do so since Wurster teaches that the Wurster-type provides a uniform coating. Further, the Wurster patent demonstrates that the Wurster-Type apparatus is not a new type of apparatus and as been known in the art since the 1940s. Therefore, it is reasonable for a skilled artisan to utilize a conventional machine routinely utilized in the pharmaceutical coating art.

Response to Amendment

The Declaration under 37 CFR 1.132 filed 7/10/06 is insufficient. For the following reasons:

The Rule 132 states that the prior art's tablets are discolored compared the instant invention and this discoloration shows a degradation of the active and is unacceptable. The standard for demonstrating that a reference is not enabling is high. The examiner points out that to demonstrate that a reference is not enabling, the applicant must demonstrate that a pellet cannot be made. Clearly, a pellet was made, regardless of the color. With regard to any showings of unexpectedness based on a 103 rejection, it is pointed out that the discoloration only appeared after an hour. Thus, the claims do not recite how long the instant pellets are stable for. Clearly, as

Art Unit: 1616

evidenced by the declaration, the pellets are stable for at least one hour. Moreover, the examiner points out that applicant's declaration is solely based on color to show degradation of the active. However, discoloration does not necessarily mean the active has degraded. The discoloration may be due to the interaction of other components. Applicant has not provided any data showing a chemical analysis of the active and its purported degradation. The mere assertion that the discoloration means that the active has degraded is not enough to show that the prior art is not stable.

Furthermore, the examiner notes that the claims are not commensurate in scope. Applicant relies on example 1 of the instant specification to demonstrate that the prior art is not enabled. Example 1 of the instant specification teaches a charged nucleus and the enteric coating with specific materials whereas the instant claims are broadly directed at least one excipient. As discussed above, applicant claims the same dosage form and states the difference between the prior art and the instant invention is the use of a separating layer. Further, applicant argues this separating layer in the prior art function to provide stability. Thus, the question is, how does applicant obtain a stable pellet by removing the stabilizing stable layer? It is noted that inventive example 1 the charged nucleus and the enteric coat comprises the components of the prior art's separating layer. For instance, the Depui's separating layer (example 4) comprises HPMC, PEG 6000, and talc whereas although the instant invention excludes the separating layer, the charged nucleus composition comprises HPMC and the enteric coating composition comprises talc.

Thus, if applicant's stability is due to adding the very components that make-up the prior art separating layer, to the charged nucleus and enteric coating respectively and thus eliminating the need for the prior art's separating layer, then applicant must claim this.

Art Unit: 1616

Further, specific excipients are utilized in specific concentrations and it is unclear if the excipient and its concentrations contribute to the stability. Lastly, the examiner notes that applicant's independent claims are drawn to several different classes of compounds and applicant emphasizes the stability of the compounds. Applicant's Rule 132 is directed to showing that a single species lansoprazole in a specific formula is stable. However, a single species cannot apply to a genus and applicant has not shown that one can formulate a stable composition with each of the claimed class of active compounds. Thus, the claims must be commensurate with the scope.

Claims 47-48 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent to Depui et al (6,365,184) in view of Wurster (2,799,241) in view of Palmo (5,232,706) in further view of Kim et al (5,219,870).

US '184 has been delineated above. The references teach mixing the proton pump inhibitor with an alkaline substance selected from sodium, potassium, calcium, magnesium and aluminum salts or phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminum hydroxide/sodium bicarbonate co precipitate; substances normally used in antacid preparations such as aluminum, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al.sub.2 O.sub.3} \cdot 0.6\text{MgO} \cdot \text{CO.sub.2} \cdot 0.12\text{H.sub.2 O}$, $(\text{Mg.sub.6 Al.sub.2 (OH).sub.16 CO.sub.3} \cdot 0.4\text{H.sub.2 O}) \cdot \text{MgO} \cdot \text{Al.sub.2 O.sub.3} \cdot 0.2\text{SiO.sub.2} \cdot \text{nH.sub.2 O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

US '184 do not teach the instant amino acid in the core material.

Art Unit: 1616

Palmo teaches an oral pharmaceutical preparation of omeprazole wherein omeprazole may be mixed with a basic compound such as sodium, potassium, magnesium, calcium, aluminum or dihydroxyaluminium salts of amino acids, such as glycocoll ($pK_{a,sub.2} = 9.6$), glutamic acid ($pK_{a,sub.3} = 9.67$) or lysine ($pK_{a,sub.2} = 8.9$, $pK_{a,sub.3} = 10.28$), or a pyridine carboxylic acid, such as nicotinic acid, or they are organic bases, such as guanidine ($pK = 12.5$) or a salt of said bases with an weak organic or inorganic acid, for example guanidine carbonate, guanidine sodium carbonate, guanidine phosphate or guanidine disodium phosphate, arginine, histidine, or lysine to achieve stabilization of omeprazole in the nucleus and to isolate it more effectively from the external acidity. See column 2, lines 25-45.

Kim teaches the use of an amino acids in general and specifically arginine, histidine, or lysine provides stability to omeprazole and prevents it from changing colors during storage. See abstract, column 3, lines 1-10, column 5-6, and example 2.

It would have been obvious to one of ordinary skill in the art at the time the invention was made combine the teachings of the above references and specifically utilize the claimed amino acids. One would have been motivated to do so with a reasonable expectation of success since Depui teaches the general use of an alkaline substance such as amino acids with the core material and the proton pump inhibitor (omeprazole) and Palmo teaches the instant amino acids are suitable for use with omeprazole to stabilize it. Furthermore, a skilled artisan would have been motivated to utilize the instant amino acids as the alkaline substance since Kim teaches amino acids, specifically arginine, histidine, or lysine provides stability to omeprazole and prevents it from changing colors during storage.

Art Unit: 1616

Claims 47-48 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent to Depui et al (6,132,771) or WO 96/01624 respectively in view of Ohno et al (4,017,647) or Wurster (2,799,241) respectively, in view of Palmo (5,232,706) in further view of Kim et al (5,219,870).

US '771 and WO '624 have been delineated above. The references teach mixing the proton pump inhibitor with an alkaline substance selected from sodium, potassium, calcium, magnesium and aluminum salts or phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminum hydroxide/sodium bicarbonate co precipitate; substances normally used in antacid preparations such as aluminum, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as Al.sub.2 O.sub.3 , 0.6MgO.CO.sub.2 , 0.12H.sub.2 O , $(\text{Mg.sub.6 Al.sub.2 (OH).sub.16 CO.sub.3}$, $0.4\text{H.sub.2}),\text{MgO.Al.sub.2 O.sub.3}$, $0.2\text{SiO.sub.2.nH.sub.2 O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

US '771 and WO '624 do not teach the instant amino acid in the core material.

Palmo teaches an oral pharmaceutical preparation of omeprazole wherein omeprazole may be mixed with a basic compound such as sodium, potassium, magnesium, calcium, aluminum or dihydroxyaluminium salts of amino acids, such as glycocoll ($\text{pKa.sub.2}=9.6$), glutamic acid ($\text{pKa.sub.3}=9.67$) or lysine ($\text{pKa.sub.2}=8.9$, $\text{pKa.sub.3}=10.28$), or a pyridine carboxylic acid, such as nicotinic acid, or they are organic bases, such as guanidine ($\text{pK}=12.5$) or a salt of said bases with an weak organic or inorganic acid, for example guanidine carbonate, guanidine sodium carbonate, guanidine phosphate or guanidine disodium phosphate, arginine,

Art Unit: 1616

histidine, or lysine to achieve stabilization of omeprazole in the nucleus and to isolate it more effectively from the external acidity. See column 2, lines 25-45.

Kim teaches the use of an amino acids in general and specifically arginine, histidine, or lysine provides stability to omeprazole and prevents it from changing colors during storage. See abstract, column 3, lines 1-10, column 5-6, and example 2.

It would have been obvious to one of ordinary skill in the art at the time the invention was made combine the teachings of the above references and specifically utilize the claimed amino acids. One would have been motivated to do so with a reasonable expectation of success since Depui teaches the general use of an alkaline substance such as amino acids with the core material and the proton pump inhibitor (omeprazole) and Palmo teaches the instant amino acids are suitable for use with omeprazole to stabilize it. Furthermore, a skilled artisan would have been motivated to utilize the instant amino acids as the alkaline substance since Kim teaches amino acids, specifically arginine, histidine, or lysine provides stability to omeprazole and prevents it from changing colors during storage.

Conclusion

All the claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1616

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Sharmila S. Gollamudi
Examiner
Art Unit 1616